A COMPREHENSIVE REVIEW ON SUSTAINED RELEASE DOSAGE FORMS USED IN THE TREATMENT OF HYPERTENSION

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ABSTRACT

Now a day's conventional dosage form is more preferred due to its flexibility of dosing and patient compliance. As a result, it is quite more effective than other dosage form. The main reason of high BP is still unknown but secondary cause of hypertension is caused due to renal endocrine or vascular lesions. High blood pressure is a major leading risk factors for demise and it may cause affliction. So, drug delivery in a proper order is necessarily preferable. Generally, a sustained release drug profile provides a steady state blood plasma level which ensures the release of drug in a predetermined rate which may be a good option for treatment of High Blood pressure at different stages. S.R. dosage form will provide a good effectiveness against the disease which is cost effective with patient satisfaction. Researchers, revealed that Sustained release formulations of different Anti- hypertensive drugs may be a good option for the treatment of High B.P. by studying different key parameters as different levels of dosage of drugs can be adjusted with minimum side effects.

Key words: Hypertension, Sustained release, High blood pressure, affliction, drug release.

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INTRODUCTION

Hypertension is a disease that is characterized by increase in blood pressure. The primary cause of hypertension is still not known but it has been assured that secondary cause of hypertension is due to vascular lesions or renal endocrine [1]. Blood pressure is generally calculated by amount of pumping of heart and resistance to blood flow in arteries. The unit of measurement of blood pressure is measured in mm/Hg namely systolic and diastolic pressure. The systolic pressure is the first or upper number which evaluates the pressures in arteries when heart beats and the diastolic pressure or lower number evaluates the

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pressure in arteries between beats. There are no such particular symptoms for hypertension but there is high risk of disease between 18-39 years of age [2]. The heart beat supplies the mechanical force which pumps the oxygenated blood to, and deoxygenated blood away from, the peripheral tissues [3].

As various classes of drugs, the common objective of treatment is to accomplish the level of steady-stage for tissue or blood which should be pharmacologically efficacious and safe for a longer duration of time [4]. The arrangement for appropriate dosage units is a paramount characteristic in achieving the objective. In the past couple of periods the controlled release technology and concept have received an improved amount recognition in today's era of evolving consciousness with respect to pharmaco-toxicity and inefficacious of drug entity when employed by using conventional methods [5]. Therefore, the drugs which are administered in the solid or semi solid dosage forms, generally shows large scale fluctuation in drug concentration within the tissues and blood stream along with subsequent amount of unacceptable toxicity with lesser effectiveness [6,7]. Fast disintegrating patches are preferred over fast disintegrating tablets as later have issues of choking and friability [7].

This consideration as well as other consideration like recurring dosing and unpredictable absorption formulated a new theory of controlled drug delivery system for therapeutic process. In controlled drug delivery system, the dosage form releases one or more drug perpetually in a predetermined format for a constant duration of time, either systemically or to a particular targetted organ . The development of drug delivery system provides a rate-controlled delivery having lesser unwanted effects, improved therapeutic potency and consistent active ingredient delivery [8].Patient acceptability and non toxicity of drugs are the essential goal that is assured by a controlled drug delivery system

Administration of controlled drug release not only implies for prolonged release time period of drug, as in the case of sustained release and prolonged release, but also implies predictability and reproducibility of drug release kinetics [9].Various Characteristics like programmed, continuous, gradual, controlled, sustained, pulsatile, fractionated, retard, deferred, slow release dosage forms and miscellaneous identical definition must be described in any one of the following definitions. Prolonged release dosage forms not only controls the release rate, but also prolongs the analeptic tissue or blood level of the drug entities for an increased time period. [10].

Controlled release dosage forms can give some restriction, whether it is a temporal or spatial nature or both type of drug release in the body or in other words, the dosage form is successful in blancing the constant drug levels in the specified cell or tissue. Retard or recurring release of dosage forms which releases the dose or a part of the dose at a time different from that immediately following administration. The probable advantages of a sustained release system that can provide us an appreciable amount of consideration for extended and efficient delivery of pharmacologically effective dosages, patient acceptability and localized treatments [11].

The bioavailability of drug entities to the sick tissue cells is controlled by a series of pharmacokinetics process-release'-absorption, distribution, metabolism and elimination in fewer cases. This approach yields inadequate bioavailability of drug molecules to the larger tissue cells [12]. The drug bioavailability to a specified cell or tissue can thus be increased while the adverse side effect to the non -

specified tissue can be decreased by implementing sustained release system principle [13]. Among various route of drug delivery Sustained release drug delivery is most widely preferred as it's less frequency of dosing and controls the release of drugs[14].

CONVENTIONAL DOSAGE FORM

The oral route for drug management constitutes the core for the eversurging branch in drug delivery technology. This technology is highly prioritized kind of dosage forms within controlled release community and patients. Inspired of huge patient acceptability, the deliveries of anti-neoplastic drugs, vaccines, proteins, etc. through the oral route are restricted as it records relatively very less bio-availability and are recorded a very low bio-availability. The oral drug dispensation should subjugate the physiological barriers i.e premature degradation, less solubility and drug permeation for attaining a sustained delivery in a streamlined manner [15].

A well-planned sustained drug release technique decreases the recurrence of drug dosing along with maintaining the concentration in blood vessels and specified tissue cells. The notable fluctuation taking place from the conventional drug administration are likely to produce zero pharmacological effect when the drug concentration drops below minimum effective dose level (med) and period of adverse reactions when the drug concentration exceeds the dose level. Drug concentration can be maintained within a narrow therapeutic range by employing sustained release system which can decrease the incident and severity of adverse side effects [16,17,18]. Advanced drug delivery systems like nano-carriers are able to improve their therapeutic efficacy by modifying their physico-chemical properties and pharmaco-kinetic properties [17].

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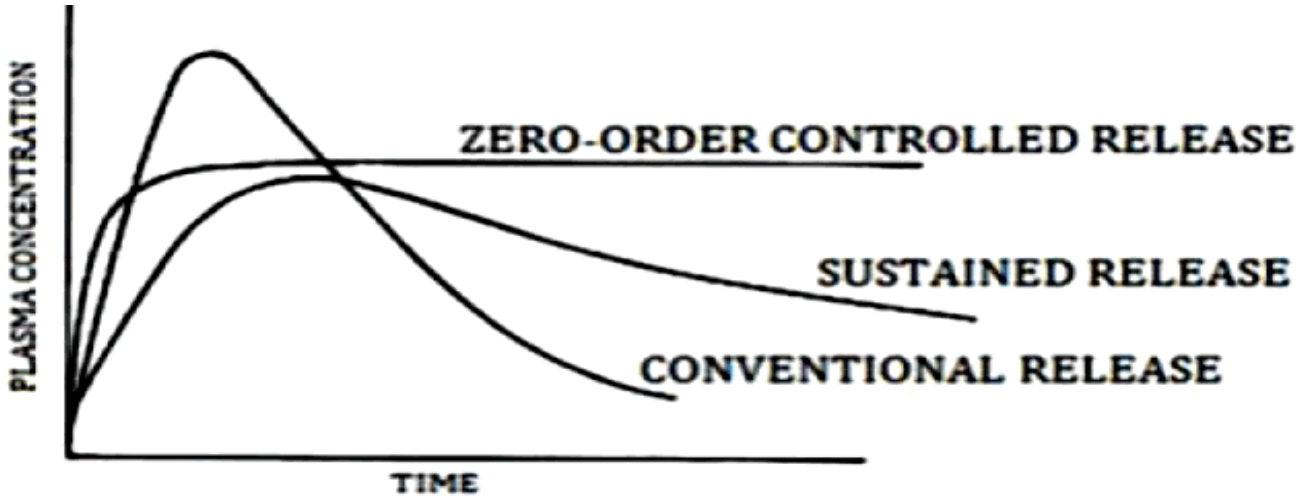

Fig.1-Plasma drug concentration profile for conventional release, a sustained release and zero order-controlled release formulations.

ADVANTAGES

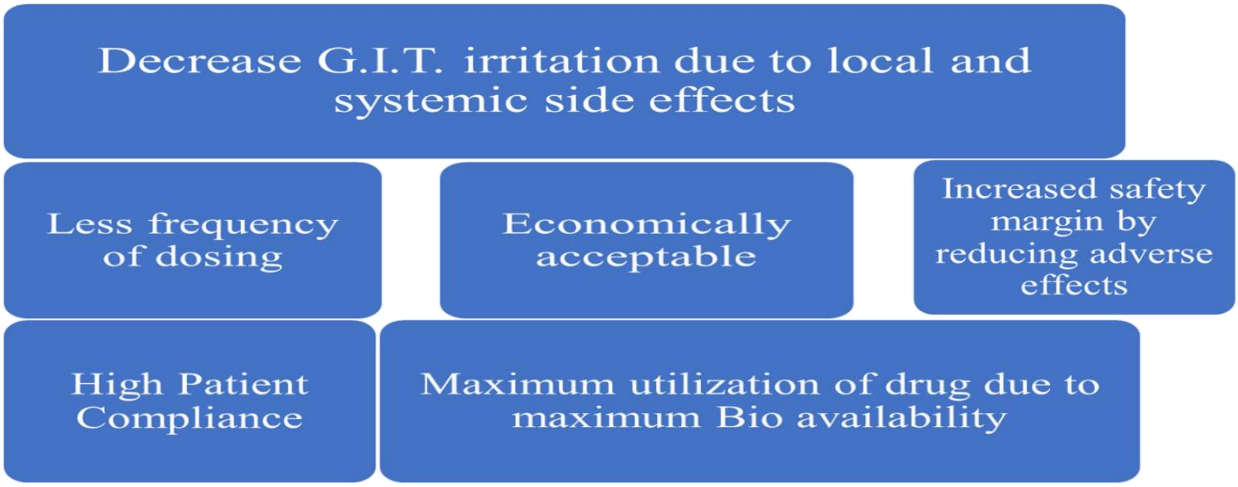

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Fig.2- Advantages of Sustained release dosage form

DISADVANTAGES

- ✓ Chance of dose dumping
- ✓ Improper potential for dose adjustment
- ✓ Cost effective
- ✓ Proper education of patient is necessary
- ✓ Poor *In-vivo* and *In-vitro* correlations

FACTORS INFLUENCING SUSTAINED RELEASE DOSAGE FORM

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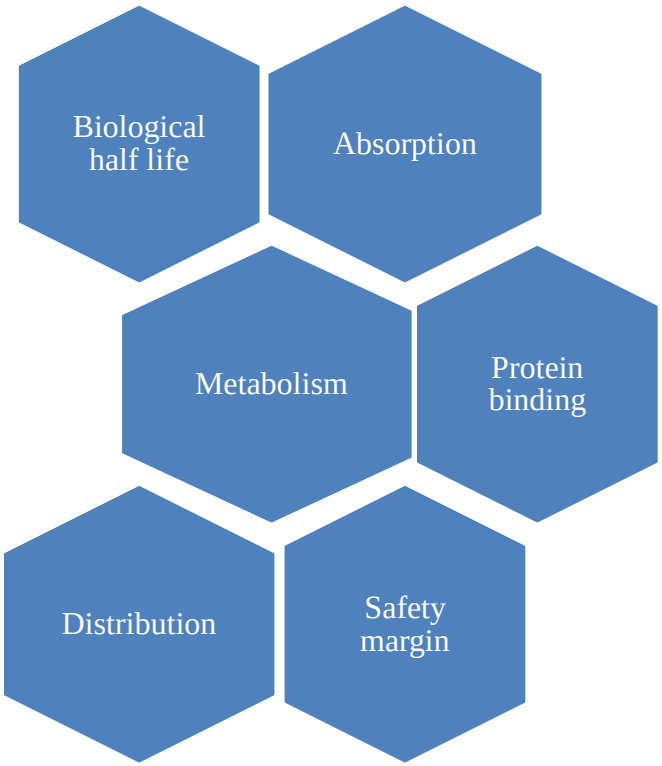

Fig.3- Factors influencing sustained release dosage form

HYPERTENSION AND IT'S SYMPTOMS [19]

Hypertension is defined as "abnormally high blood pressure," therefore it is often referred as high blood pressure.

Blood pressure consists of two numbers. The first pressure or systolic pressure is the pressure which exhibits on blood vessels when the heart contracts or beats. The second number or the diastolic pressure is the pressure which exhibits on the vessels of the heart which rests between beats.

Hypertension is investigated on evaluating for two different days, the readings for the systolic blood pressure and diastolic blood pressure on both days should be ≥140 mmHg and ≥90 mmHg respectively.

Generally, there are no particular mentioned symptoms but few symptoms of hypertensions are seen which include headaches shortness of breath or nosebleeds.

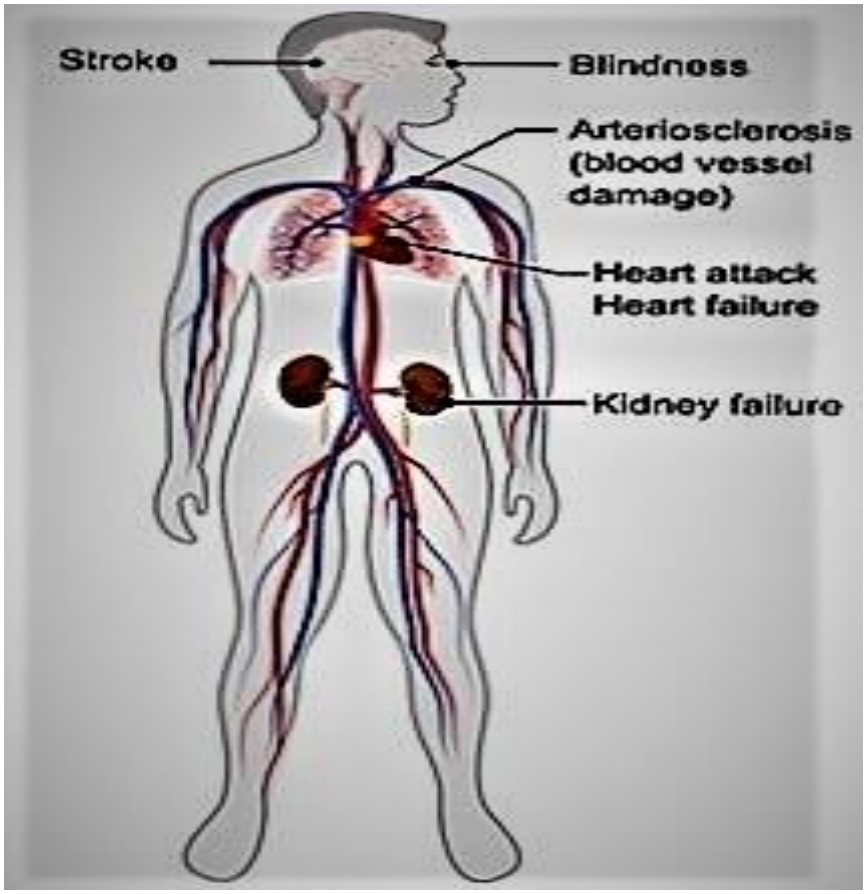

Fig.4- Symptoms of Hypertension

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PATHOPHYSIOLOGY OF HYPERTENSION

Hypertension is characterized as severe rise of blood pressure therefore causing an increased morbidity and mortality. Here Vascular tone may be increased due to α- adnereceptor stimulation or high release of peptides like Epinephrines and Norepinephrines. The terminal route shows an elevated amount of systolic calcium within the vascular smooth muscle leading to vaso constriction. Various growth factors like angiotensin and endothelins causes a rise of mass in smooth vascular muscles known as vascular

remodeling. Elevation of systemic vascular resistance and vascular stiffness argument the load imposed on the left ventricle, which further causes dysfunction hypertrophy and diastolic function in the left ventricular region.

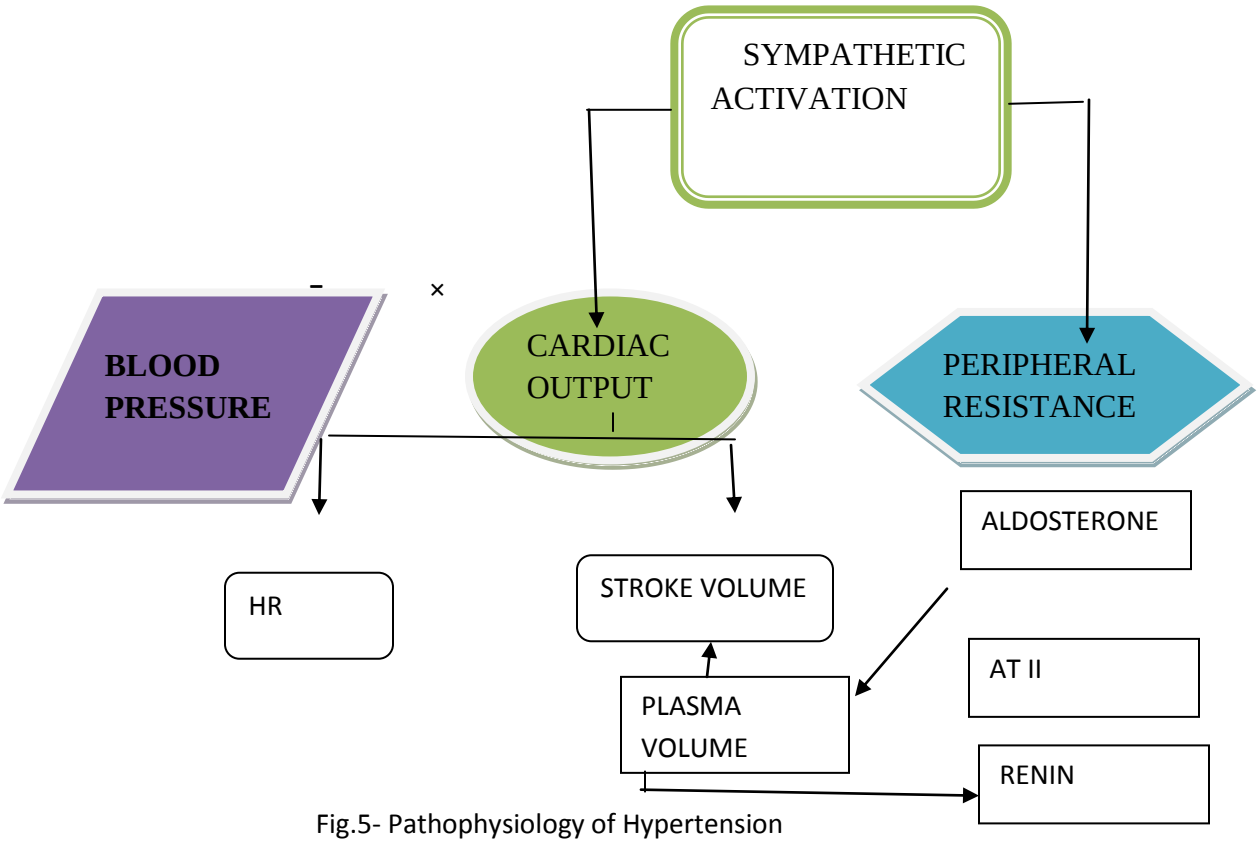

Fig.5- Pathophysiology of Hypertension

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HYPERTENSION STAGES [20]

Normal: Systolic pressure is less than 120 mm Hg and diastolic pressure is less than 80 mm Hg.

Elevated: Systolic pressure ranges between 120-129 mm Hg and diastolic pressure is less than 80 mm Hg.

Stage 1: Systolic pressure ranges between 130-139 mm Hg or diastolic pressure ranges between 80-89 mm Hg.

Stage 2: Systolic pressure is at least 140 mm Hg or diastolic pressure is at least 90 mm Hg.

CLASSIFICATION OF ANTI HYPERTENSIVE DRUGS [21]

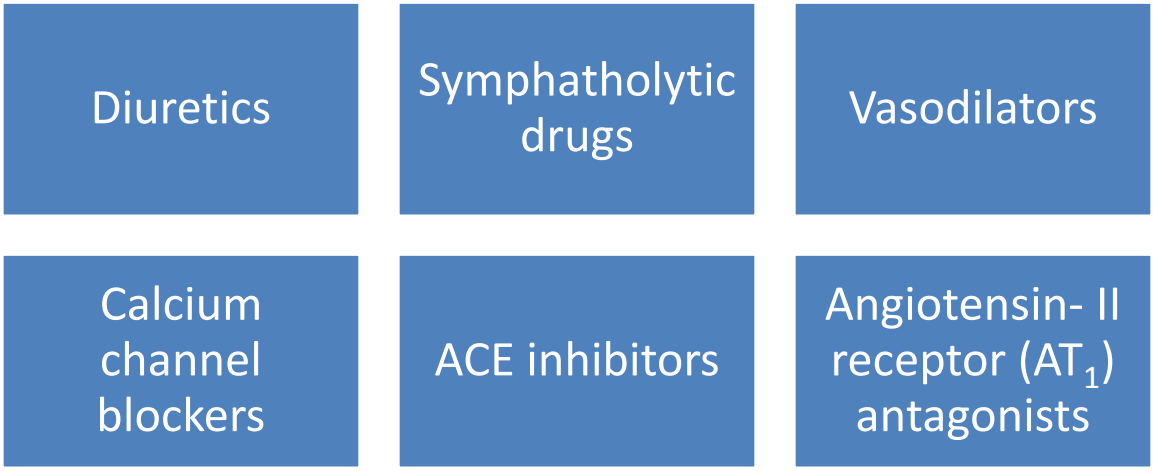

Fig.6- Classification of Antihypertensive drugs

- Diuretics (Hydrochlorothiazide, frusemide, triamterene, spironolactone)
- Symphatholytic drugs (Methyldopa, clonidine, guanabenz, guanfacine, trimethaphan, guanethidine, reserpine, propranolol, metoprolol, atenolol, parazosin, labetolol, carvedilol)
- Vasodilators (Hydralazine, minoxidil, diazoxide, fenoldopam, sodium nitroprusside)
- Calcium channel blockers (Verapamil, nifedipine, diltiazem, nicardipine, felodipine)
- ACE inhibitors (Trandolapril, quinapril, fosinopril)
- Angiotensin- II receptor (AT_1) antagonists (Losartan, Candesartan)

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MECHANISM OF ACTION OF ANTI HYPERTENSIVE DRUGS[22,23]

- Diuretics- It lower the blood pressure by decreasing body's sodium store. They also cause a decrease in peripheral vascular resistance by their direct vasodilating properties.
- Symphatholytic drugs- It act predominantly by decreasing sympathetic activity in the brain and cardiovascular system.
- Vasodilators- The exact mechanism is still unknown. It reduces total peripheral resistance without mediation by adrenergic, cholinergic or histaminic receptors.
- Calcium channel blockers- It involves interference with the calcium entry into myocardial lowering the availability of intracellular calcium. Calcium channel blockers cause smooth muscle relaxation by lowering intracellular calcium availability. Calcium channel blockers cause smooth muscles relaxation on which vascular muscle appears to be more sensitive but other muscles like bronchiolar, gastro-intestinal and uterine are also relaxed. It acts on cardiac muscles by reducing cardiac contractility and cardiac output in a dose dependent fusion. It acts on peripheral blood vessels by decreasing peripheral resistance and blood pressure in systemic as well as pulmonary arteries.
- Angiotensin Converting Enzyme (ACE) Inhibitors- ACE inhibitors inhibit the transformation of Angiotensin I to Angiotensin II which is a potent arterial vasoconstrictor and has sodium retaining property. ACE inhibitors lower systemic systemic vascular resistance and mean systolic & diastolic blood pressure in hypertension.

- Angiotensin (AT_1) receptor Antagonists- Angiotensin II acts through particular cell surface receptors. AT_1 & AT_2 are the two subtypes of Angiotensin receptor that are identified. Much of the biological effects of angiotensin II are mediated by AT_1 receptors. These have been recently developed as potential hypertensive agents.

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IMPORTANCE OF SUSTAINED RELEASE IN HYPERTENSION

- *Mathur et al., (20*13) have developed sustained release tablets of Verapamil Hydro Chloride employing Eudragit RS100, methyl cellulose, ethyl cellulose, carboxymethyl cellulose and hydroxypropyl methyl cellulose . A total of eight formulations were made and compared with marketed drug subjected to *In-vitro* drug release study. This study showed F6 have a good drug release i.e. 99.16% on 12 hours of *In-vitro* dissolution study. [24]
- *Ashutoshkumar et al; (2010)* have developed sustained release tablets of Metoprolol Succinate using synthetic polymers like HPMC K-100. A total of six formulations were prepared. *In-vitro* drug release study have shown thet F6 have 95.5% of drug release in 20 hours which shows a good release profile for a sustained release dosage form. [25]
- *Choudhari et al., (2018)* have developed directly compressible (DC) co-processed excipient which is proficient in delivering almost zero order drug release profile along with modified component was developed devoid of any synthetic modifications by employing numerous procedures like spray drying, high shear mixer granulation and physical mixing. Co-processed excipient was progressed when employed the release inhibiting polymer namely Eudragit RSPO, independently, in addition with various concentration of HPMC 100 cps, Ethyl cellulose and Hydroxyl propyl cellulose . From the eighteen combinations of concentrations, the nine co-processed excipient showed favourable flow properties which are found appropriate for direct compression and further developed into tablets. A BCS Class I drug - Metaprolol succinate, was selected as a choice for model drug. *In vivo* pharmacokinetic study of optimized formulation in rats showed similar pharmacokinetic behavior as was observed with the marketed brand (Selekon® 200 mg). Study revealed that co-processed excipient has advantage over polymers with single property and can be utilised for sustained release formulation. [26]

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- *Xiaopeng et al., (2013*) have prepared Sustained release Diltiazem hydrochloride (DTZ) pellets by extrusion-spheronization method. Methacrylic acid and ethylcellulose coating formulations were employed to make the DTZ pellets sustained release. The pellets with the best coating copolymer were subjected to pharmacokinetic studies in beagle dogs. The dissolution profiles of pellets coated with Eudragit NE30D were similar to marketed Herbesser. The relative bioavailability of DTZ sustained release capsules compared with Herbesser was 98.5 ± 36.4%. All the data indicated self-made sustained pellets could prolong the release of DTZ, decrease the fluctuation of drug level *in vivo* and increased the compliance of patients. [27]
- *Dey et al., (2014)* have formulated sustained release matrix tablets of Atenolol using retardant Polymers which were derived from *Xanthomonas campesteris* and *Cyamopsis tetragonolobus.* To optimize the formulation, 3^2 factorial design was employed where content of polymer blend (X_1) and ratio of xanthan-guar gum were considered as independent variables. Total 9 formulations were made. The *in vivo* pharmacokinetic parameters of the optimized formulation were compared with marketed sustained release formulation of atenolol (Aten®). From the

release profile, it was observed that the xanthan gum-guar gum ratio influenced the drug release from the tablets. Varying the amount of polymer blends from F1 to F9 affected the drug release from the tablets. As the amount of polymer blend increased from 10% to 20%, the drug released was decreased due to increase in resistance for penetration of water into tablet matrix. It was concluded that F8 was optimized formulation which have the potential to give sustained delivery of atenolol to improve bioavailability of drug. [28]

- Hussain *et al;* (2014) have developed sustained release tablets of Acyclovir by direct compression method. All the formulations i.e. F1-F13 were subjected for *in-vitro* dissolution studies. Similarity factor analysis was carried out for all the formulations with similarity factor (f2) values greater than 50 were considered as optimized formulations. F3, F8 and F13 have shown sustained release activity for 12 hours. FTIR studies were conducted which proved that there is no physical incompatibility present between drug and excipients. [29]
- Patil *et al;* (2017) have developed sustained release matrix tablets of Atenolol which contains natural polymers like Moringa oleifera, Guar and Xanthan gum. A total of eight formulations were made. *In-vitro* dissolution study shown that F7 have sustained release activity up to 15 hours. [30]
- Sahu *et al;* (2017) have formulated sustained release tablets of Atenolol using natural polymers like guar gum and Chitosan. A total of five formulations were prepared and all the formulations were subjected to *In-vitro* dissolution study. F4 have shown a highest release of 83.50% up to 12 hours. [31]
- Manavalan *et al;* (2003) have developed sustained release tablets of Diltiazem Hydrochloride using Methocel, Ethyl cellulose, Eudragit which was proceed towards *In-vitro* study. A total of 10 formulations were prepared and *In-vitro* study was conducted for 12 hours. The study revealed that DSR 10 shown a good release profile as compared to other formulations. [32]

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- Chakrahari.*et al;* (2011) have formulated sustained release tablets of Losartan using both hydrophobic and hydrophilic polymers. A total of nine formulations were prepared and were subjected to *In-vitro* dissolution study for 10 hours and stability study. The study revealed that F3 have a good release profile as compared to other formulations and shown a good stability profile i.e. 3 months. [33]
- Yan *et al;* (2000) have developed Nifedipine HPMC sustained release tablets. Both *In-vitro* and *In-vivo* study were conducted. The study was conducted over 24 hours. The study revealed that there was a good *In*-vivo/ In-*vitro* correlationship in all the formulations. The Loo-Riegelman method was found to be suitable for estimation of *In-vivo* cumulative drug absorption.[34]
- Rahman *et al;* (2013) have formulated sustained release matrix tablets of Verapamil Hcl using polymers like Eudragit RSPO, PEC and HPMC K4M by direct compression method. *In-vitro* studies were carried out using 0.1 N Hcl and pH 7.2 for 12 hours. A total of nine formulations were developed out of which F2 have shown 90% drug release which contains Eudragit RSPO. The release profile of the formulation was found to be better in Alkaline medium as compared to acidic medium and the study suggests that desired drug release profile can be achieved by employing a systematic approach for formulations. [35]

CONCLUSION

The current review suggests that SR dosage form may be a novel approach in the treatment of Hypertension which will provide a good patient compliance with minimum side effects with proper dosing. Hence, the current review recommends for more research works to be conducted for developments of formulations with Antihypertensive activity which will be more effective than the current available formulations.

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